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Rates of Down Syndrome at Livebirth by One-Year Maternal Age Intervals in Studies With Apparent Close to Complete Ascertainment in Populations of European Origin: A Proposed Revised Rate Schedule for Use in Genetic and Prenatal Screening

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Precision and accuracy in determining rates of Down syndrome at livebirth are indispensible to algorithms which determine eligibility for prenatal cytogenetic diagnostic services. We derived Down syndrome rates by single year of maternal age which we propose as a revised rate schedule for background risk. Data on European-origin populations were obtained from 5 sources judged most likely to have complete ascertainment of cases. A "constant plus exponent" regression model and variants extending the analysis to higher powers of maternal age were applied to several ranges of maternal age. Confidence intervals about the rates were calculated. This analysis results in rates significantly higher than those in widespread use though the confidence intervals show a need for caution in assuming precision. Sources of variation in rates are also considered.

KEY WORDS: Down syndrome, chromosome abnormality, genetic counseling, prenatal diagnosis, ascertainment

INTRODUCTION

The need for accurate maternal age-specific rates of Down syndrome has taken on much greater clinical and public health significance with the recent increased use of prenatal biochemical screening for this defect. Prior to such screening, differences among the published studies reporting rates of Down syndrome in livebirths by 1 year maternal age interval had little clinical impact. Indeed some reports preferred to present the range in rates at each age to accommodate apparent variation among studies [e.g., Hook, 1981]. Sources of such variation could be unknown risk factors both biological and environmental (whose prevalence varies temporally and/or geographically), differences in the completeness and accuracy of studies, and statistical fluctuation, all considered further below.

However, the application of biochemical screening to prenatal diagnosis has sharpened the need for exact maternal age-specific rates. In many centers today, a pregnant woman will only receive diagnostic cytogenetic amniocentesis if her risk of a Down syndrome livebirth is greater than or equal to some threshold risk, usually the rate regarded as equivalent to that of the average 35-year-old woman [Hook, 1994]. A background maternal age-specific risk is multiplied by the relative risk implied by results from biochemical screening and the adjusted risk compared with the threshold, as described, for example, in Cuckle et al. [1987] and Tabor et al. [1987].

One approach to the conundrum of various rate schedules in the literature has been to use the (weighted) average of the results of all reports on Down syndrome by single year of maternal age. Such an approach assumes that the differences among studies are attributable *only* to statistical fluctuation. Cuckle et al. [1987] in fact applied this approach to 8 published studies, taking a weighted average of the separate risk estimates and then performing a regression analysis. They have also extended these results by presenting rates by 1 month intervals [Cuckle et al., 1989]. Elsewhere [Hecht and Hook, 1994], we have examined this methodology closely. As we noted, if the analysis is restricted to the 2 studies among the eight included which on separate grounds were judged most likely to have been complete, then the resulting rates at ages over 36 are significantly higher than those in the widely used

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schedules of Cuckle et al. and, moreover, the magnitude of this difference increases with age.

Here we extend the analysis to include additional data reporting results by 1 year maternal age interval in which, as we judge from reported methods, ascertainment appears likely to be close to complete.

MATERIALS AND METHODS

Data

All data sources known to us, in which rates of Down syndrome by 1 year maternal age interval were available or could be obtained after adjustment for induced prenatal loss, were subjected to review (by one of us, CAH) of the reported methodology without reference to the rates presented in each work. After judgments about how complete ascertainment was likely to be, we limited our further analyses to the studies described in Appendices A and B. Two of the studies, from South Belgium [Koulischer and Gillerot, 1980] and from Sweden [Hook and Lindsjö, 1978], as noted above, were also included in the pooling by Cuckle et al. [1987]. We extended these by including more recent data from, respectively, Koulischer et al. [1991] and Lindsten et al. [1981] (a further study of Down syndrome in Sweden similar to the Lindsjö work). Studies termed "Intensive Newborn" (see Appendix A) should provide complete ascertainment through cytologic testing of every livebirth, despite small numbers. A study from South Australia [Staples et al., 1991] appeared likely to have achieved complete ascertainment once data from one 5-year interval had been excluded. Comparing the results including and excluding each particular study, we excluded one from the final synthesis for reasons indicated in "Results" below.

Selective induced abortion was corrected for by assuming that the probability that any such case resulted in a livebirth was 0.7 [Hook, 1983]. Details with regard to some further adjustment of the South Belgium data appear in Hecht and Hook [1994], which only considered data sets analyzed in Cuckle et al. [1989].

Appendix B provides the corrected Down syndrome data and observed rates for the selected studies and the pooled data set (reflecting the one exclusion as noted in "Results").

The pooling of the data in these studies assumes in essence that there are no significant spatiotemporal differences in rates of Down syndrome, an assumption we discuss further below.

The Rationale of the Regression Analysis

A number of different regression equations may be used to model rates of Down syndrome over the entire maternal age interval [see Lamson and Hook, 1980]. We derived smoothed Down syndrome rates by fitting a "constant plus exponential" (CPE) equation. Thus the basic function is modeled as

$$y = a + \exp\{f(x)\} \tag{1}$$

where y is the rate in livebirths and $f(x)$ is a linear polynomial in x, maternal age. This model expresses an age-independent component of Down syndrome rates (stemming from gonadal mosaic parents, translocations, etc.) in the constant, a, and an age-dependent component in the exponential portion of the equation. Although $f(x)$ is a linear function of age, the expression for rate cannot be reexpressed as a linear function as it could be, for instance, if we ignored the age-independent term a and took logarithms. Thus, the equation is less tractable than the more traditionally used equations in many other regression analyses which are "linear" in their modeling of the rates of events or the log or logistic of rates.

The subtypes of the function used are

$$y = a + \exp\{b_0 + b_1(x)\}, \text{ the 3-parameter model,} \tag{2}$$

$$y = a + \exp\{b_0 + b_1(x) + b_2(x^2)\}, \text{ the 4-parameter model,} \tag{3}$$

$$y = a + \exp\{b_0 + b_1(x) + b_2(x^2) + b_3(x^3)\}, \text{ the 5-parameter model,} \tag{4}$$

$$y = a + \exp\{b_0 + b_1(x) + b_2(x^2) + b_3(x^3) + b_4(x^4)\}, \text{ the 6-parameter model.} \tag{5}$$

We undertook analyses of up to 6 parameters for all data sets considered.

The simplest equation, type (2), with 3 parameters, has been used previously in many analyses. This does impose certain conditions on the data set analyzed: the rates must increase monotonically as an (exponentially) linear function of age. Thus, this equation does not allow for a leveling off (or even decline) of rates at the upper extreme of age nor a possible increase with age at the lower boundary of age. The possibility of both such trends has been suggested previously [see Ferguson-Smith, 1983; Ferguson-Smith and Yates, 1985; Hook et al., 1984; Hook, 1985]. This equation, if imposed on the data set, should be used over age ranges in which such a monotonic increase may be safely inferred, from say ages 20 to 45. The main advantage of this expression is that with only 3 parameters it is perhaps the simplest equation that can be made to fit the data. Confidence intervals derived for this model will be narrower than those derived using more complex models.

The equation of type (3) with 4 total parameters does allow a leveling off of rates (or decline or increase) at one *or* the other extreme of age, but not both, i.e., does allow one point of inflection in the regression curve.

The 5 parameter equation [type (4)] allows a leveling off (or decline or increase) of rate with age at *both* extremes of maternal age. Thus, it imposes fewer conditions than any of the simpler models upon the nature of the curve's changes with age. The models do not impose a *direction* in any change in the curve at the extremes of age. If rates showed a steeper increase with oldest ages and/or steeper decrease at youngest ages, despite the trends reported in the literature, it would be reflected in the analysis. The penalty paid with increasing numbers of parameters is less precision in the estimates, i.e., wider confidence intervals, despite the greater flexibility in allowing for changes in the trends.

The introduction of 6 terms [equation (5)] enables adjustment for a further point of inflection at some interior section of the curve.

Statistically, the relative improvement of fit by adding more parameters may be evaluated by the

Akaike Information Criterion (AIC). In general, this states that if the difference in the likelihood ratio statistic, G^2, between any two models is greater than twice the difference in the degrees of freedom associated with each model (or number of parameters), then the more complex model is preferable. Otherwise, the simpler model should be chosen. In many of our analyses below, this criterion would lead to our choosing the simpler 3-parameter model. Nevertheless, to allow for changes at the extremes of age, we also present rates derived for the 5- and 6-parameter models. For reasons considered in the Discussion, in general we think the rates derived from a more complex model to be preferable. *Illustrative data* comparing the predictions of the 3-, 5-, and 6-parameter models for the maternal age range 17 to 49 appear in Table I.

The choice of ages to be included in the regression analysis is an additional issue. Concern that a significant component of reported data at ages 50 and over and under 15 reflects reporting errors [see discussion in Hook et al., 1984] prompted us to confine all analyses to ages 15 to 49. Within this range we undertook analyses on age 15–49, 20–49, 15–45, 20–45, and other ranges such as 17–49. Many regression analyses in the 15 to 49 range, especially with 5 and 6 parameters, would not converge, but analyses in slightly truncated ranges, e.g., from age 17 and above, would do so.

We present 90% confidence intervals about all derived rates. These give one-tailed 95% confidence limits. A clinician in any particular case is usually concerned with whether a younger client's rate is above or an older client's rate is below, some particular threshold. If one is concerned about the probability of such a particular outcome at the 0.05 level, then the one-tailed 95% confidence limit is appropriate and is given by the boundaries of the 90% confidence interval.

RESULTS

Table I presents the results of various regression analyses for selected maternal ages in the 17 to 49 year range. (The raw data on which these analyses were carried out appear in the appendix.) This notes variation in derived rates using 3, 5, or 6 parameters for particular studies and combinations of studies pooled. There were so few data in the "intensive newborn" studies that only the 3-parameter analysis converged. These data contributed only a small proportion of the total in any event. Among the other studies, the effect of increasing the number of parameters was most noticeable at the older ages. In general, as the number of parameters increased, the derived rates in the older ages tended to diminish. (At ages under 40 there was relatively little effect.) Comparisons of the likelihood ratio statistics between different models generally indicated

TABLE I. Comparison of Rates per 1,000 Livebirths Predicted at Selected Ages by Different Studies, Using Regression Models with 3, 5, or 6 Parameters, Derived for Maternal Ages 17–49

Maternal age	Intensive newborn[a]	South Belgium			Sweden 1968–70			Sweden 1971–77		
	3	3	5	6	3	5	6[b]	3	5	6
17	.66	.66	.72	c	.70	.70	.66	.65	.65	.66
20	.66	.68	.72	c	.71	.71	.68	.67	.67	.66
30	.80	1.17	1.10	c	1.09	1.09	1.13	1.24	1.24	1.34
35	1.77	2.89	2.95	c	2.57	2.53	2.44	3.14	3.11	2.77
40	9.84	10.23	10.74	c	9.45	9.58	9.56	10.99	11.13	11.86
45	76.79	41.66	35.84	c	41.56	41.58	43.21	43.51	43.18	38.75
47	178.10	74.02	55.16	c	76.37	72.61	67.84	76.32	72.21	28.84
49	d	131.91	82.27	c	140.83	122.10	87.92	d	d	d
G^2	33.753	47.617	46.186		26.148	25.764	25.055	36.529	35.413	27.636
df	28	30	28		30	28	26	28	26	25

Maternal age	Subtotal pooled			S. Australia			All		
	3	5	6	3	5	6	3	5	6[b]
17	.67	.66	.57	.59	.66	.65	.65	.66	.61
20	.68	.68	.65	.62	.67	.66	.67	.68	.66
30	1.18	1.18	1.19	1.13	1.03	1.04	1.17	1.14	1.16
35	2.92	2.89	2.81	2.70	2.75	2.74	2.87	2.86	2.78
40	10.39	10.53	10.68	8.66	9.84	9.86	9.96	10.38	10.53
45	42.49	42.01	41.93	31.39	24.65	24.67	39.45	36.97	36.89
47	75.63	71.03	62.32	53.20	29.20	28.37	69.31	57.07	50.34
49	134.99	116.17	78.03	90.44	29.94	27.32	122.14	82.62	56.66
G^2	41.625	40.333	38.319	31.754	26.161	26.143	41.686	38.077	34.908
df	30	28	27	30	28	27	30	28	26

[a]Did not converge for 5 and/or 6 parameters.
[b]Did not converge for 6 parameters using age range 17–49; 6 parameter results using age range 18–49 are presented in above table (rate for age 17 extrapolated from regression on ages 18–49).
[c]Did not converge for 6 parameters using age ranges 17–49, 17–48; converged for regression on ages 19–49 and values for above cells were (3 parameters) .67, .68, 1.17, 2.87, 10.23, 41.93, 74.73, and for age 49, 133.57; G^2 46.91, 28 df. (5 parameters) .75, .75, 1.07, 2.98, 10.71, 35.93, 58.09, and for age 49, 95.31; G^2 44.995, 26 df. (6 parameters) .77, .76, 1.04, 3.02, 10.74, 35.17, 66.61, and for age 49, 160.19; G^2 44.083, 25 df.
[d]Data collected only through age 47.

that simpler models, i.e., those with 3 or 4 parameters, were "acceptable." However, the trends cited above indicated to us that the safest course was to use regression analyses with 6 parameters to adjust for an effect at the upper extremes of age that otherwise would be missed.

One may note also in Table I a relatively consistent difference between the rates in South Australia and the others. In general, rates were lower in the Australian group, and the difference became more marked with advancing age. At age 45, the rates per 1,000 livebirths in the Australian data ranged from 24.7 to 31.4, but from 35.8 to 76.7 in the analyses of all others; there was no overlap. The results at other older ages indicated the same trend.

The limitations of the regression analyses at the youngest extremes of age prevent us from exhibiting in Table I another interesting difference between the Australian rates and those in the other studies. At ages 15 and 16 the rates are notably higher in South Australia than in the others (see Appendix B). There were 5 observed cases of Down syndrome among 4,830 livebirths born to mothers aged 15 or 16 in Australia (1.0 per 1,000) compared to 1 in 9,444 livebirths in all the other studies pooled (0.1 per 1,000). (At age 15 the values were 1/1,182 vs. 0/1,235 and at age 16, 4/3,648 vs. 1/8,209.) Another point of interest about these observed rates at 15 and 16 in South Australia but not in the other studies is that they are higher at these ages than in the immediately older ages.

These differences may reflect some underlying true difference in rates, or else other factors. We consider these points further below in the Discussion.

On the basis of the above analyses, we chose conservatively to construct a summary rate schedule derived from results of the 6-parameter analysis, excluding the South Australian data. Derived and observed rates at all ages appear in Table II, as well as 90% confidence intervals about the derived rates. The reader may note in Table I for selected ages the difference made by including or excluding the South Australian data, or by using other sets of parameters.

Regression coefficients and standard errors are provided in Table III for the regression analysis on maternal ages 17 to 49, with 3, 5, and 6 parameters, for each data set. (In some cases the age range was truncated to achieve convergence and coefficients are provided for these regressions.) From these the reader may calculate projected rates at any age for any selected set of data, including or excluding the Australian data. In the interests of space, coefficients and derived values for four parameters are not given but will be provided on request.

DISCUSSION

Any attempt to derive future risks of disorders by pooling data from various sources assumes implicitly that ascertainment of cases by all studies has been accurate and complete and only statistical fluctuation contributes to any variation in the data. For the analysis here this amounts to assuming that for Down syndrome there are no significant spatiotemporal variations in rates in the data considered, aside from those adjusted for, namely maternal age and selective termination of pregnancy following prenatal diagnosis of Down syndrome. It is still possible that all of the studies included, except for those from the small "intensive newborn" series, had significant underascertainment of cases, even though the rates are higher here than in the excluded studies. We can only note, first, that a capture–recapture analysis of the Swedish data for 1971–1977 [Lindsten et al., 1981; see also Morton and Lindsten, 1976] suggested that ascertainment was very close to complete, and these rates are not markedly discrepant from those in the other series. Second, the rates in the newborn series in which complete ascertainment is highly likely do not suggest any markedly greater rates than those in the other selected studies.

We cannot explain the apparent differences in rates between the South Australia study and the others. We note that while consistent, these differences are relatively subtle and only noteworthy at the extremes of age. Of interest is that the rates deviate in the direction toward the average rate of those of all ages, going up as age diminishes to the extreme and going down or at least leveling off as age advances to the extreme. This may reflect a true difference in the rate of Down syndrome at the extremes of age in South Australia compared to the other areas.

Another factor that would explain this trend in the South Australian data is random error in reporting of ages. Of course there is likely to be some random error in any reporting of data. Random age errors for a disorder whose true rates increase with age, and in which the denominators of rates (i.e., in the number of livebirths) are much smaller at the extremes of the distribution would tend to produce an artifactual leveling or diminishment of rate at the upper ages and an artifactual leveling or rise in rate at the lowest ages. In essence the artifactual outcomes, the deviation at each extreme toward the average rate, result from an effect similar to a "regression to the mean." A significant proportion of random reporting errors in maternal age in one study compared to others would produce this difference between them, although such leveling effects would be present in every study to at least some extent if there are random age errors. (For a detailed discussion as to how such random errors in the reporting of the disorder at any age can produce such an apparent systematic change noticeable in the rates at the extremes of age, see Hook et al. [1984].)

Again we emphasize that we cannot state that such an effect in fact accounts for the difference between South Australia and the other studies, only that the effect is consistent with the observations. One cannot exclude the possibility that there is a true difference in rate between South Australia and other jurisdictions primarily at the extremes of age.

There is relatively little evidence to date for consistent variation among populations in maternal age-specific rates at least among those of European origin. All of the rates analyzed in this study are from those primarily of ancestral European background. There is suggestive evidence of higher maternal age-specific

TABLE II. Down Syndrome Data, Observed Rates, and Derived Rates per 1,000 Livebirths, by Single Year of Maternal Age, Pooled Data* (Derived Over Maternal Ages 17–49, 6-Parameter Model, With 90% Confidence Intervals)†

Maternal age	Cases/ livebirths	Observed rates	Derived rates	90% CI
15[a]	0/1,235	0	.51	[b]
16[a]	1/8,209	0.12	.54	[b]
17	10/20,439	0.49	.57	.37, .78
18	23/36,566	0.63	.60	.48, .72
19	37/58,113	0.64	.63	.55, .71
20	43.4/76,753	0.57	.65	.59, .72
21	81/95,167	0.85	.68	.61, .75
22	81/111,315	0.73	.70	.64, .77
23	82/124,577	0.66	.73	.68, .79
24	100/133,699	0.75	.76	.71, .81
25	98.7/136,190	0.72	.80	.75, .85
26	102/132,095	0.77	.84	.79, .90
27	123.7/119,835	1.03	.90	.84, .96
28	96/106,173	0.90	.97	.91, 1.04
29	113/91,477	1.24	1.07	1.00, 1.13
30	96.4/76,304	1.26	1.19	1.12, 1.26
31	81/61,082	1.33	1.35	1.27, 1.43
32	85.1/49,803	1.71	1.57	1.47, 1.67
33	55/40,400	1.36	1.87	1.73, 2.00
34	72.7/32,789	2.22	2.27	2.09, 2.44
35	63.8/26,074	2.45	2.81	2.60, 3.03
36	73.9/20,321	3.64	3.56	3.31, 3.82
37	81.6/15,636	5.22	4.60	4.29, 4.92
38	87/12,873	6.76	6.03	5.62, 6.44
39	74/9,469	7.81	8.00	7.42, 8.57
40	81.4/6,665	12.21	10.68	9.83, 11.53
41	53.2/4,915	10.82	14.29	13.05, 15.52
42	65.1/3,057	21.29	19.06	17.32, 20.81
43	37.8/1,966	19.23	25.21	22.76, 27.67
44	38.5/1,052	36.61	32.86	29.15, 36.57
45	24.4/509	47.97	41.93	35.66, 48.19
46	16/268	59.70	52.03	40.85, 63.20
47	3/81	37.04	62.32	42.88, 81.77
48	3/25	120.00	71.53	39.77, 103.30
49	0/10	0	78.03	30.05, 126.01
Total observations	2,084.7/1,615,142			

*Pooled data from intensive newborn studies [Evans, 1974; Hamerton, 1974; Ratcliffe, 1977], Koulischer and Gillerot [1980], Koulischer [1980, 1992], Koulischer et al. [1991], Hook and Lindsjö [1978], Lindsten et al. [1981], and Lindsten [1980], inclusive.
†Correction for selective abortion yields decimals; see text for description of all corrections. Decimals in denominators rounded to nearest whole number for purposes of table (but not in computer calculations); observed rates calculated from nonrounded numbers.
[a]Rates for ages 15 and 16 extrapolated from regression on ages 17 through 49.
[b]Confidence intervals not calculated for point estimates out of age range of regression analysis.

rates in Israelis of non-European origin [Hook and Harlap, 1979] and in Latinos in Southern California [Wilson et al., 1992] but not in other groups yet analyzed. [For references and data on this point see Hook and Porter, 1977, and Hook, 1994.]

Maternal cigarette smoking has been reported to be negatively associated with Down syndrome livebirths, in at least some studies [e.g., Hook and Cross, 1985], but neither this nor any other environmental factor has yet been documented conclusively as a risk factor for the disorder. If such a factor is documented then there will be a need to construct rate schedules adjusting for both age *and* smoking (or other risk factor).

The rates we have derived here deviate in some significant respects from those of the widely used rate schedules of Cuckle et al. [1987]. That analysis used studies whose results were readily available in the literature. The results of our derived rate schedule find essentially no difference in rates at age 20. For ages 25 through 35 the schedule here predicts rates about 7 to 8% higher; at age 40 the rates are about 20% higher and at age 45, 17% higher than those predicted by Cuckle et al. (Above age 45 the difference diminishes and even reverses because Cuckle et al. used a 3-parameter model which predicts a continuing unmodulated increase with age whereas our 6-parameter model

TABLE III. Regression Coefficients (and Standard Errors) for All Analyses Presented*

Data set, age range, number parameter	a (SE)	b_0 (SE)	b_1 (SE)	b_2 (SE)	b_3 (SE)	b_4 (SE)
Intensive newborn,	.0006616	−21.6139792	.4230815			
17–47, 3 parameter	(.0002217)	(5.4818983)	(.1306685)			
S. Belgium 17–49,	.0006471	−16.2809111	.2908237			
3 parameter	(.0000556)	(.6926632)	(.0178185)			
S. Belgium, 17–49,	.0007154	−25.4026285	.8143896	−.0085866	.0000307	
5[a] parameter	(.0001039)	(49.808506)	(3.8833825)	(.1005512)	(.0008645)	
S. Belgium, 19–49,	.0006559	−16.3428801	.2923433			
3 parameter	(.0000572)	(.7000512)	(.0179810)			
S. Belgium, 19–49,	.0007495	−41.3924842	2.0358725	−.0395354	.0002907	
5 parameter	(.0000836)	(58.924767)	(4.5695759)	(.1175961)	(.0010042)	
S. Belgium, 19–49,	.0007454	47.3045849	−7.9532276	.3771274	−.0073433	.0000519
6 parameter	(.0000763)	(71.061907)	(8.4077494)	(.3685058)	(.0070639)	(.0000500)
Sweden 1968–70, 17–49,	.0006930	−17.0625942	.3081150			
3 parameter	(.0000649)	(.8483753)	(.0210712)			
Sweden 1968–70, 17–49,	.0006349	−4.4918327	−.6664145	.0250828	−.0002141	
5 parameter	(.0001824)	(15.123483)	(1.1435922)	(.0296292)	(.0002605)	
Sweden 1968–70, 18–49,[b]	.0006588	−50.1675906	4.6899776	−.2065619	.0041651	−.0000306
6 parameter	(.0002282)	(114.64856)	(12.122177)	(.4820056)	(.0085167)	(.0000563)
Sweden 1971–77, 17–47,	.0006377	−15.9373158	.2841715			
3 parameter	(.0000517)	(.5686663)	(.0146484)			
Sweden 1971–77, 17–47,	.0005499	−5.2588344	−.5398009	.0211746	−.0001809	
5 parameter	(.0001454)	(7.4538882)	(.6022871)	(.0169562)	(.0001620)	
Sweden 1971–77, 17–47,	.0006591	−240.025947	26.6677029	−1.1489934	.0219427	−.0001551
6 parameter	(.0000560)	(118.60928)	(13.362017)	(.5599073)	(.0103415)	(.0000710)
Subtotal pooled, 17–49,	.0006540	−16.2971684	.2916285			
3 parameter	(.0000325)	(.3874381)	(.0098764)			
Subtotal pooled, 17–49,	.0005900	−5.9800214	−.5125705	.0208560	−.0001797	
5 parameter	(.0000967)	(6.9093761)	(.5305454)	(.0139949)	(.0001256)	
Subtotal pooled, 17–49,	.0003533	−21.9647716	1.9777067	−.1060169	.0024915	−.0000201
6 parameter	(.0008054)	(9.6901534)	(1.4860813)	(.0783728)	(.0016475)	(.0000122)
S. Australia, 17–49,	.0005777	−15.5215265	.2675923			
3 parameter	(.0000571)	(.6564411)	(.0168725)			
S. Australia, 17–49,	.0006428	−5.9186938	−.8239962	.0371802	−.0003953	
5 parameter	(.0001056)	(25.731329)	(1.9961835)	(.0517683)	(.0004483)	
S. Australia, 17–49,	.0006370	−11.7324948	−.0608703	.0014218	.0003230	−.0000053
6 parameter	(.0001308)	(53.042436)	(6.1999396)	(.2760367)	(.0054369)	(.0000396)
All, 17–49, 3 parameter	.0006345	−16.0869543	.2852891			
	(.0000282)	(.3318021)	(.0084751)			
All, 17–49, 5 parameter	.0006077	−4.9917074	−.6658617	.0268627	−.0002497	
	(.0000710)	(6.4318596)	(.4988190)	(.0132116)	(.0001185)	
All, 18–49,[b] 6 parameter	.0005359	−21.3900806	1.6718044	−.0883455	.0021461	−.0000180
	(.0005530)	(26.806530)	(2.2143053)	(.0858125)	(.0017261)	(.0000133)

*Values for G^2 appear in Table I.
[a]Regression on ages 17–49 and 18–49 did not converge for 6 parameters.
[b]Regression on ages 17–49 did not converge for 6 parameters.

could allow a leveling off in the rate.) Our own view is that the rates presented here are preferable for use as "prior" rates in biochemical screening.

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NOTE ADDED IN PROOF

While this manuscript was in press, Dr. Andrew Carothers kindly pointed out to us one aspect of the Edinburgh newborn series which leads to a very slight upward bias by including it. This study selectively included male births and, as is well known, the sex ratio in Down syndrome, about 1.2, is higher than that in the general population, about 1.06. We estimate the selective inclusion of males has led to two more cases of Down syndrome in this study than would otherwise have occurred. Thus, a better estimate of the total number of affected individuals in the subtotal is 2,082.5 not 2,084.5. The effect of this upon derived rates is negligible.

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APPENDIX A. CHARACTERISTICS OF SELECTED DOWN SYNDROME STUDIES

Study	Data sources	False positives	Selective abortions	Corrections
"Intensive Newborn": Winnipeg, Canada, 1970–73 [Evans, 1974; Hamerton, 1974; study described in Hamerton et al., 1975] and Edinburgh, Scotland, 1967–72 [Ratcliffe, 1977; study described in Jacobs et al.,1974]	Hospital studies: cytogenetic testing of every livebirth	None	None	None needed
S. Australia: 1965–89 [Staples et al., 1991]	Down syndrome cases identified through 2 birth defect registers registers and council providing services to mentally retarded persons	Not discussed in original article	Information on all 46 terminations provided in original article	Each selective abortion multiplied by 0.7 [Hook, 1983] and added to cases at appropriate maternal age; denominators adjusted accordingly; data for the years 1960–65 were excluded following the suggestion of Staples et al. [1991] that this could have been a period of under ascertainment[a]
S. Belgium: 1971–90 [Koulischer and Gillerot, 1980; Koulischer et al., 1991]	Hospital studies: cytogenetic testing for every baby showing any sign of Down syndrome	None	Information on all 31 terminations provided [Koulischer, 1980, 1992]	Each selective abortion multiplied by 0.7 [Hook, 1983] and added to cases at appropriate maternal age; denominators adjusted accordingly; 3 neonatal deaths of cases after birth added at appropriate maternal ages [Koulischer, 1980] [see Hecht and Hook, 1994]
Sweden: 1968–70 [Hook and Lindsjö, 1978; study described in Lindsjö, 1974], 1971–77 [Lindsten et al., 1981]	Down syndrome records collected from all pediatric and gynecologic services, all other services for mentally retarded, all cytogenetic labs in country (1968–7)]; from 3 national registers with 83% analyzed cytogenet ically (1971–77)	Cases without positive cytogenetic workup or with ambiguous clinical picture discarded	None (1968–70); information for all 40 terminations (1971–77) provided [Lindsten, 1980]	None needed (1968–70); corrected for selective abortion (1971–77) as described above

[a]We amended the data given in the article by excluding the data for the years prior to 1965. Cases were subtracted according to information provided by Dr. Staples [1992]. In order to exclude total livebirths for the time period we used the *Statistical Register of South Australia* [Aitchison, 1964, 1965a, 1965b, 1966, 1967]. Information by single year of maternal age is given for confinements, not livebirths, while information for multiple births is given by maternal age quinquennium, so it was necessary to apportion multiple births over order one to each single year in the quinquennium, to obtain figures for livebirths at each maternal age for the years 1960–64. One Down syndrome case recorded as "unknown" for maternal age was distributed over all ages, weighted by the maternal age structure.

APPENDIX B. DOWN SYNDROME DATA AND OBSERVED RATES PER 1000 LIVEBIRTHS, BY SINGLE YEAR OF MATERNAL AGE, FROM SELECTED STUDIES

	Intensive newborn studies[a]		South Belgium[b]		Sweden 1968–70[c]		Sweden 1971–77[d]	
Maternal age	Cases/ livebirths	Obs rates	Cases/ livebirths	Obs rates	Cases/ livebirths	Obs rates	Cases/ livebirths	Obs rates
15	0/55	0	0/797	0	0/383	0		
16	0/228	0	0/2,681	0	1/1,979	0.51	0/3,321	0
17	0/457	0	4/5,834	0.69	3/5,265	0.57	3/8,883	0.34
18	0/799	0	5/10,664	0.47	10/9,212	1.09	8/15,891	0.50
19	1/1,013	.99	9/18,405	0.49	4/13,433	0.30	23/25,262	0.91
20	1/1,288	.78	15.4/24,929	0.62	10/17,267	0.58	17/33,269	0.51
21	2/1,539	1.30	33/31,302	1.05	16/21,133	0.76	30/41,193	0.73
22	0/1,727	0	27/36,613	0.74	19/24,584	0.77	35/48,391	0.72
23	0/1,909	0	27/41,692	0.65	23/26,862	0.86	32/54,114	0.59
24	0/2,146	0	32/44,895	0.71	19/27,747	0.68	49/58,911	0.83
25	1/2,113	.47	29.7/44,385	0.67	22/27,525	0.80	46/62,167	0.74
26	1/1,945	.51	34/43,811	0.78	23/25,016	0.92	44/61,323	0.72
27	1/1,771	.56	47.7/38,488	1.24	16/21,694	0.74	59/57,882	1.02
28	4/1,594	2.51	23/33,604	0.68	18/18,623	0.97	51/52,352	0.97
29	1/1,333	.75	35/28,804	1.22	17/15,888	1.07	60/45,452	1.32
30	2/1,113	1.80	28.4/23,932	1.19	11/13,835	0.80	55/37,424	1.47
31	1/883	1.13	15/18,342	0.82	21/11,541	1.82	44/30,316	1.45
32	2/748	2.67	24.1/15,369	1.57	10/9,578	1.04	49/24,108	2.03
33	1/598	1.67	15/13,082	1.15	16/7,861	2.04	23/18,859	1.22
34	0/488	0	26.7/10,672	2.50	14/6,672	2.10	32/14,957	2.14
35	0/400	0	22/8,802	2.50	11/5,413	2.03	30.8/11,459	2.69
36	1/331	3.02	33.2/6,465	5.14	12/4,648	2.58	27.7/8,877	3.12
37	1/307	3.26	26.8/4,755	5.64	18/3,917	4.60	35.8/6,657	5.38
38	0/260	0	33.2/4,415	7.52	16/3,129	5.11	37.8/5,069	7.46
39	3/192	15.63	19.1/3,030	6.30	16/2,415	6.63	35.9/3,832	9.37
40	0/144	0	29.7/2,069	14.35	22/1,805	12.19	29.7/2,648	11.22
41	2/96	20.83	13/1,700	7.65	17/1,343	12.66	21.2/1,776	11.94
42	2/61	32.79	19.7/921	21.39	15/845	17.75	28.4/1,230	23.08
43	0/49	0	10/625	16.00	6/527	11.39	21.8/765	28.50
44	0/12	0	10/292	34.25	13/360	36.11	15.5/388	40.00
45	2/19	105.26	4/112	35.71	9/161	55.90	9.4/217	43.38
46	1/7	142.86	3/74	40.54	7/82	85.37	5/105	47.62
47	1/2	500.00	1/3	333.33	1/35	28.57	0/41	0
48			1/6	166.67	2/19	105.26		
49			0/3	0	0/7	0		
Total obs	31/25,627		656.7/521,573		438/330,804		959/737,139	

	South Australia[e]		Subtotal: all but Australia		Total: all	
Maternal age	Cases/ livebirths	Obs rates	Cases/ livebirths	Obs rates	Cases/ livebirths	Obs rates
15	1/1,182	0.85	0/1,235	0	1/2,417	.41
16	4/3,648	1.10	1/8,209	.12	5/11,857	.42
17	4/8,019	0.50	10/20,439	.49	14/28,458	.49
18	6.1/13,069	0.46	23/36,566	.63	29.1/49,635	.59
19	13/18,017	0.72	37/58,113	.64	50/76,130	.66
20	12/22,687	0.53	43.4/76,753	.57	55.4/99,440	.56
21	24/28,203	0.85	81/95,167	.85	105/123,370	.85
22	18/32,919	0.55	81/111,315	.73	99/144,234	.69
23	24/37,717	0.64	82/124,577	.66	106/162,294	.65
24	35.1/40,204	0.87	100/133,699	.75	135.1/173,903	.78
25	31.1/41,008	0.76	98.7/136,190	.72	129.8/177,198	.73
26	32.7/39,812	0.82	102/132,095	.77	134.7/171,907	.78
27	25/36,590	0.68	123.7/119,835	1.03	148.7/156,425	.95
28	34.5/32,964	1.05	96/106,173	.90	130.5/139,137	.94
29	17.7/28,605	0.62	113/91,477	1.24	130.7/120,082	1.09
30	24.7/23,902	1.04	96.4/76,304	1.26	121.1/100,206	1.21
31	26/19,819	1.31	81/61,082	1.33	107/80,901	1.32
32	17/15,810	1.08	85.1/49,803	1.71	102.1/65,613	1.56
33	22.4/12,563	1.79	55/40,400	1.36	77.4/52,963	1.46
34	26.4/10,083	2.62	72.7/32,789	2.22	99.1/42,872	2.31

(continued)

APPENDIX B. DOWN SYNDROME DATA AND OBSERVED RATES PER 1000 LIVEBIRTHS, BY SINGLE YEAR OF MATERNAL AGE, FROM SELECTED STUDIES (*continued*)

	South Australia[e]		Subtotal: all but Australia		Total: all	
Maternal age	Cases/ livebirths	Obs rates	Cases/ livebirths	Obs rates	Cases/ livebirths	Obs rates
35	21.5/8,345	2.58	63.8/26,074	2.45	85.3/34,419	2.48
36	22.5/6,248	3.61	73.9/20,321	3.64	96.4/26,569	3.63
37	21.5/4,840	4.45	81.6/15,636	5.22	103.1/20,476	5.04
38	31.6/3,880	8.13	87/12,873	6.76	118.6/16,753	7.08
39	12.8/2,935	4.37	74/9,469	7.81	86.8/12,404	7.00
40	23.2/2,043	11.37	81.4/6,665	12.21	104.6/8,709	12.02
41	15.1/1,466	10.33	53.2/4,915	10.82	68.3/6,381	10.71
42	12/941	12.78	65.1/3,057	21.29	77.1/3,998	19.29
43	16.4/659	24.92	37.8/1,966	19.23	54.2/2,625	20.66
44	8.7/367	23.78	38.5/1,052	36.61	47.2/1,419	33.29
45	5/206	24.34	24.4/509	47.97	29.4/715	41.15
46	2/111	18.06	16/268	59.70	18/379	47.51
47	1/34	29.46	3/81	37.04	4/115	34.80
48	1/18	55.64	3/25	120.00	4/43	93.06
49	0/11	0	0/10	0	0/21	0
Total obs	593/498,925		2,084.7/1,615,142		2,677.7/2,114,067	

*Correction for selective abortion and unknown maternal age (S.Australia) yields decimals; see Appendix A for description of all corrections. Decimals in denominators rounded to nearest whole number for purposes of table (but not in computer calculations); observed rates calculated using nonrounded numbers.

[a]Includes data sets as described in Appendix A; no corrections needed.

[b]Data from Koulischer and Gillerot [1980], Koulischer [1980, 1992], and Koulischer et al. [1991]; corrected for selective abortions and 3 neonatal deaths.

[c]Data from Hook and Lindsjö [1978].

[d]Data from Lindsten et al. [1981] and Lindsten [1980]; corrected for selective abortion.

[e]Data from Staples et al. [1991] and Staples [1992]; data prior to 1965 excluded and data corrected for selective abortion and one case with unknown maternal age.